ANDES PEDIATRICA
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Andes pediatr. 2024;95(5):608-612
DOI: 10.32641/andespediatr.v95i5.5092

CLINICAL CASE

Beyond premature apnea pauses: congenital myotonic dystrophy type 1

Más allá de las pausas de apnea en el prematuro: distrofia miotónica tipo 1 congénita

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Received: January 5, 2024; Approved: Jul 4, 2024

What do we know about the subject matter of this study?

Congenital myotonic dystrophy type 1 (CMD1) is characterized by hypotonia, respiratory compromise, facial diplegia, poor feeding, arthrogryposis, and hyporeflexia. Its diagnosis requires a high index of suspicion and can be a diagnostic challenge for pediatricians, especially if other processes such as prematurity coexist.

What does this study contribute to what is already known?

The initial manifestations of CMD1 can go unnoticed in the preterm newborn, as manifestations such as apneas, respiratory compromise, and feeding difficulties overlap. Early diagnostic orientation based on key points of the anamnesis and physical examination will help us to direct complementary tests, adapt the management of complications, as well as provide genetic counseling.

Abstract

Congenital myotonic dystrophy type 1 (DM1) is a rare entity that can pose a diagnostic challenge, especially if other processes such as prematurity coexist. **Objective**: to describe the typical presentation of congenital DM1 and thus increase diagnostic suspicion. **Clinical Case:** A 29-week preterm female newborn who required non-invasive mechanical ventilation until 41 weeks postmenstrual age; she presented with apnea requiring manual ventilation with a self-inflating bag and cardiac massage. Initially, it was attributed to prematurity, but on physical examination, hypotonia, hyporeflexia, bilateral Achilles tendon retraction, facial diplegia, and weak sucking were confirmed. These characteristics, together with the respiratory compromise, suggested a possible congenital neuromuscular disease. The patient's history included infertility in the mother and polyhydramnios during gestation. The examination of the mother showed clinical myotonia, later confirmed by electromyogram, which suggested congenital myotonic dystrophy. This was confirmed genetically, finding 2000 CTG copies in the newborn and 833 in her mother. **Conclusions:** Apneas and respiratory compromise in a hy-

Keywords:
Newborn;
Apnea;
Myotonic Dystrophy;
Genetic Anticipation;
Premature Newborn

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How to cite this article: Andes pediatr. 2024;95(5):608-612. DOI: 10.32641/andespediatr.v95i5.5092

potonic and weak newborn are a frequent manifestation of this disease. The presence of myotonia in the mother of a newborn with suspected neuromuscular disease should lead us to think of congenital DM1. This case highlights the importance of an exhaustive anamnesis and physical examination of the patient and her mother as key elements in the etiological diagnostic orientation.

Introduction

Apnea of prematurity is a consequence of the immaturity of the breathing regulation mechanisms in preterm newborns[1]. Although prematurity is the most frequent cause, its diagnosis is of exclusion. Therefore, and especially if they persist after reaching 37 weeks postconceptional age, other etiologies should be considered. These include neuromuscular diseases, which can cause respiratory problems, from apnea to respiratory failure.

Myotonic dystrophy type 1 (MD1) is the most common neuromuscular disease in adults, with a prevalence of 1:8000 worldwide[2]. However, in its congenital form, it is rare, with a prevalence ranging according to studies from 2.1 to 28.6 per 100,000 live births[3,4,5]. It is caused by the CTG triplet repeat expansion in the myotonic dystrophy protein kinase (*DMPK*) gene, located on chromosome 19q[6]. It is transmitted by autosomal dominant inheritance, although more than 90% of congenital cases are of maternal origin, probably due to greater meiotic instability during ovogenesis[7]. Its clinical manifestations have a wide spectrum of severity and age of presentation since they depend ultimately on the extent of CTG triplet repeat expansion, which in numbers greater than 34 is markedly unstable, causing the affected infant to inherit repeat lengths greater than those present in the parent. This phenomenon is called clinical anticipation and results in increased disease severity and an earlier age at the onset in successive generations[8].

Those with a number of CTG repeats between 35 and 49 are asymptomatic; those between 50 and 150 will manifest as mild myotonia or weakness, and those with up to 1000 copies will present the classic phenotype, which associates multisystemic alterations such as arrhythmias, insulin resistance, infertility, or cataracts[9].

The congenital form is the most severe phenotype, with more than 1000 recurrences, and its manifestations include global hypotonia, respiratory failure, feeding difficulties, and polyhydramnios[9].

The objective of this report is to describe the typical presentation of CMD1, and thus increase diagnostic suspicion in a premature newborn, highlighting the usefulness of screening in her/his mother.

Clinical Case

Preterm female newborn of 920 grams at 29+1 weeks of gestation by emergency cesarean section due to risk of loss of fetal well-being and suspicion of maternal chorioamnionitis. She is the first child of non-consanguineous parents, with no known diseases so far, nor history of previous miscarriages. However, the presence of infertility in the mother stands out, requiring up to 4 cycles of in vitro fertilization to achieve gestation. The pregnancy was controlled and presented moderate polyhydramnios. After premature rupture of membranes and onset of uterine dynamics, two doses of prenatal corticosteroids were administered for lung maturation and neuroprotection with magnesium sulfate before delivery. The patient presented hyaline membrane disease, which was managed with surfactant administration and invasive mechanical ventilation until 7 days of life. Subsequently, she was maintained on noninvasive mechanical ventilation until 85 days of life, beyond 41 weeks postmenstrual age, presenting striking difficulty in withdrawing respiratory support. In addition, she presented frequent and severe apneas of mixed characteristics (obstructive and central), some of which required resuscitation with a bag valve mask and cardiac massage.

The physical examination revealed severe hypotonia and muscle weakness, with lower limbs in the frog position, hyporeflexia, and bilateral Achilles tendon retraction, as well as facial diplegia with an inverted V-shaped upper lip, characteristics that initially could have gone unnoticed due to the gestational age and the difficulty of examination due to the clinical instability of the patient, but later became evident in the various serial physical examinations. In addition, at 35 weeks of corrected gestational age, difficulty in oral feeding was noted, not attributable to prematurity, with difficulty in removing the nasogastric tube.

Considering the maternal history of infertility, the history of polyhydramnios during gestation, and the physical examination of hypotonia, facial diplegia, and arthrogryposis, the possible presence of a neuromuscular disease was considered.

A complete neurological examination was then performed on the parents, finding in the mother clinical signs of myotonia (showing slow relaxation of the fingers and hand after normal muscle contraction),

something she did not perceive as symptomatic, as it allowed her to lead a normal life.

Following this finding, the mother underwent an electromyogram, which showed a pattern of myotonic discharges that, in the clinical context of the patient, suggested CMD1. Given these results, a directed genetic study was requested, which found 2,000 CTG copies in the newborn, and 833 copies in her mother, confirming both the definitive diagnosis of CMD1, as well as explaining the different clinical expressivity between them according to the genetic anticipation phenomenon.

Discussion

MD1 includes different presentations, being the congenital form the most severe of them, presenting a mortality of up to 30-40%, mainly due to respiratory failure[10].

Among the clinical features, infertility is a typical characteristic in women with MD1[11], as well as polyhydramnios (related to swallowing weakness), which can be found in up to 17-25% of cases and often indicates severe fetal involvement[12,13]. Reduced fetal movements are also common. In addition, an increased risk of prematurity has been reported, up to 30-50%[13], which may be due to polyhydramnios[14].

At birth, it is characterized by global hypotonia and severe weakness, as well as respiratory insufficiency, both due to respiratory muscle weakness and central dysfunction[9,15]. In addition, they typically present with other signs of weakness such as facial diplegia with a characteristic inverted V-shaped upper lip (present in up to 80%) and elongated facies due to atrophy of the temporalis and masseter muscles, as well as hyporeflexia, arthrogryposis of the ankles with clubfoot (an indicator of lack of mobility in early fetal development), and difficulty in oral feeding, with the need for a nasogastric tube in many cases[7,16].

Apneas are frequent respiratory events in this disease, associated with significant respiratory compromise, which is the main cause of death in the neonatal period, and the most important prognostic factor. In this respect, prematurity also plays an important role in the prognosis, due to the increased risk of pulmonary complications that it entails[13]. Up to 70-80% of patients will require mechanical ventilation[3], indicated when there is hypoventilation or apnea. While the use of bilevel positive airway pressure (BiPAP) is the first option, continuous positive airway pressure (CPAP) should be used when there is a predominantly obstructive component in respiratory failure[17]. It should be noted that in some cases, apnea may be so significant that it causes a hypoxic brain injury, which makes the clinical picture of encephalopathy predominate, erroneously orienting to hypoxic-ischemic encephalopathy, overlooking CMD1[12].

In the presence of neonatal respiratory failure that cannot be explained by respiratory pathology or prematurity, we should explore the possibility of neuromuscular diseases, such as spinal muscular atrophy, congenital myopathies, and congenital muscular dystrophies. Specifically, when facing a case of global hypotonia with respiratory failure, apneas, facial diplegia, and feeding difficulties, CMD1 should be considered, regardless of gestational age[18].

Myotonia, both clinical and electrical, is not usually present in the first year of life[12], so it is not a finding we will look for in the neonate. However, it is an essential feature in adults and can easily be observed on a simple directed physical examination, with slow relaxation of the fingers and hand following normal muscle contraction in a "handshake". It is not uncommon for an adult, usually the mother, to be diagnosed with CMD1 after giving birth to an affected newborn, underscoring the possibility of a subclinical presentation of this disorder[12]. Because of this, upon suspicion of CMD1, the mother should be thoroughly examined, as her physical examination may be revealing and key to etiologic diagnostic guidance, as was the case presented in this report.

Early recognition of the disease in preterm infants can help us not to force the withdrawal of ventilatory support or nasogastric tube feeding as would be expected in a healthy patient, as well as to initiate rehabilitative therapies early, with the prognostic implications that this entails. Early diagnosis is also crucial for adequate genetic counseling, as multiple family members are often affected, and early counseling allows for surveillance and early intervention in these, as well as appropriate family planning[2].

Conclusions

In a neonate with persistent respiratory distress and apneas after prematurity, it is important to consider a possible neuromuscular disease, especially CMD1, when signs of hypotonia, facial diplegia, arthrogryposis, feeding difficulties, and history of polyhydramnios and infertility coexist.

This autosomal dominant entity, although severely manifested in the newborn, may go unnoticed in the mother as it can be oligosymptomatic. However, the clinical signs of myotonia are easy to demonstrate in a simple "handshake" examination.

Having a high index of clinical suspicion based on the anamnesis and physical examination is crucial to direct the complementary tests and reach a diagnosis

as early as possible, with the consequent prognostic importance that this entails.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Acknowledgments

Hospital Fundación Alcorcón for facilitating the research activity.

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